X=Y–ZH Systems as Potential 1,3-Dipoles. Part 11.[1] Stereochemistry of 1,3-Dipoles Generated by the Decarboxylative Route to Azomethine Ylides

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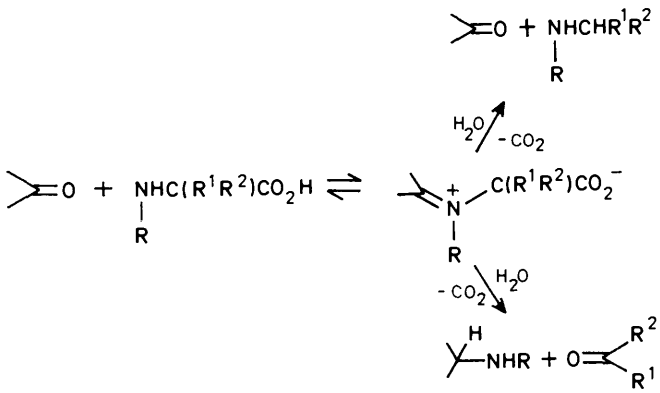
The decarboxylative reaction of aryl aldehydes with cyclic secondary α-amino acids or primary α-amino acids in the presence of *N*-methyl- or *N*-phenyl-maleimide leads, *via* an intermediate azomethine ylide, to mixtures of bicyclic pyrrolidine cycloadducts in good yield. Cyclic secondary α-amino acids, where the carboxylic group is non-benzylic, give cycloadducts arising from a stereospecifically generated *anti*-dipole. Acyclic α-amino acids, and cyclic secondary α-amino acids with the carboxylic group located at a benzylic site, give rise to cycloadducts derived from both *anti*- and *syn*-configurations of the intermediate azomethine ylides. The reactions show little discrimination between *endo*- and *exo*-transition states for the cycloadditions.

The degradation of primary and secondary α-amino acids and α,α-disubstituted α-amino acids to aldehydes and ketones, with concomitant decarboxylation, on heating with carbonyl compounds (Scheme 1) is known as the Strecker Degradation.[2]



Scheme 1.

The analogous biochemical process is usually mediated by enzymes which employ pyridoxal (Vitamin B_6) as the prosthetic group[3] although several examples are known which employ pyruvate.[4]

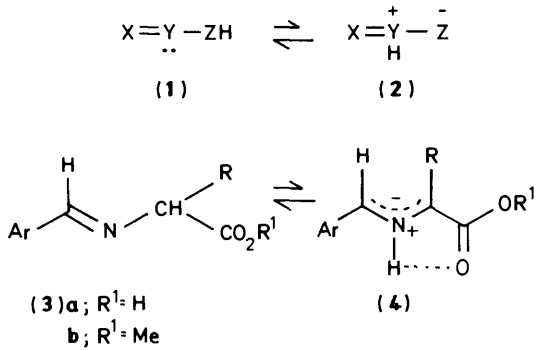
Model studies of the biochemical processes by Herbst *et al.*[5] provided the first evidence of the formation of mixtures of carbonyl products. Thus *p*-methoxyphenylalanine and pyruvic acid were found to react in boiling water to give both *p*-methoxybenzaldehyde and acetaldehyde. Snell *et al.*,[6] and Lawson *et al.*,[7] concluded that model carbonyl components replacing pyridoxal should possess an aromatic nucleus with *ortho*-formyl and -hydroxy groups and should in addition contain a strong electron-withdrawing group in the *ortho* or *para*-position to the formyl group, *e.g.*, 4- and 6-nitro-2-hydroxybenzaldehyde. However, Schonberg and Moubacher's[2] extensive studies of carbonyl compounds capable of effecting the Strecker Degradation showed many other types of carbonyl compound were effective.

Little synthetic use had been made of the Strecker Degradation prior to our work.[1,8–10] Rizzi[11] used the Strecker Degradation to reductively aminate substituted benzaldehydes using α-ethylalanine as the amino group donor (Scheme 2). Takano *et al.* reported an efficient synthesis of tryptamine by Strecker Degradation of tryptophan using catalytic amounts of

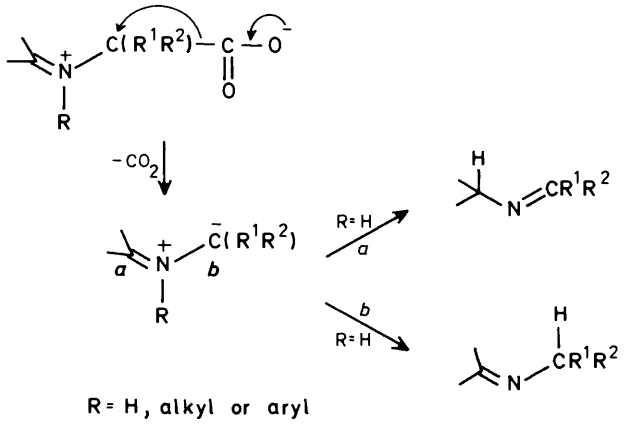
Scheme 2.

a range of carbonyl compounds.[12] Recently Hashimoto *et al.*[13] described the use of 1% cyclohex-2-enone in cyclohexanol at 154 °C to catalytically decarboxylate α-amino acids to the corresponding amines in 73—95% yield.

Our interest in the Strecker Degradation developed from our general studies of 1,2-prototropy in X=Y–ZH systems (**1**) ⇌ (**2**).[14] We have shown that imines of both α-amino acids (**3a**) and α-amino acid esters (**3b**) give rise to 1,3-dipoles (**4a**) and (**4b**) respectively on heating in a range of solvents.[16,17] This and other considerations[1,8] led us to suggest a revised mechanism for the Strecker Degradation involving an intermediate azomethine ylide (Scheme 3). The new mechanism was readily



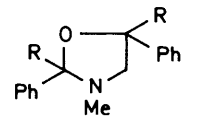
testable by experiments designed to trap the intermediate azomethine ylide. Trapping experiments were immediately successful and cycloadducts with a range of dipolarophile were obtained in good to excellent yields. Azomethine ylides were shown to be generated in a range of solvents [chloroform, acetonitrile, methanol, benzene, toluene, dimethylformamide (DMF), *etc.*] at temperatures ranging from room temperature to 140 °C. All α-amino acids (primary and secondary, cyclic and acyclic, α,α-disubstituted) except tertiary α-amino acids were shown to undergo the reaction.[1,8–10] In the absence of a dipolarophile, and when R = H (Scheme 3), the intermediate azomethine ylide undergoes kinetically controlled prototropy



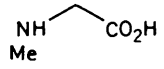
Scheme 3.

to the neutral imine. The final site of the proton is dependent on the negative charge density at *a* and *b* in the intermediate azomethine ylide (Scheme 3). Subsequently we became aware that Rizzi had obtained a low yield (1 and 27% respectively) of oxazolidines (**5a** and **b**) on heating the *N*-alkyl-amino acid sarcosine (**6**) with benzophenone or benzaldehyde at 170 °C.[15] He suggested (**5a** and **b**) had arisen *via* cycloaddition of the carbonyl compound to either the azomethine ylide (**7a** and **b**) or the aziridine (**8a** and **b**). The severe conditions and low yield apparently deterred further study.

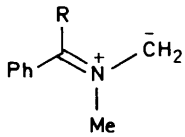
In our original communication[8] we remarked on the somewhat capricious dependence of the intermediate azomethine ylide's stereochemistry on the structure of both the carbonyl component and the dipolarophile. This observation contrasted with the situation observed in the 1,2-prototropy route to azomethine ylides (**3**) ⇌ (**4**) where the kinetically formed



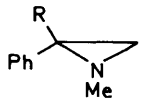
(**5**) **a**; R = Ph
b; R = H



(**6**)



(**7**)



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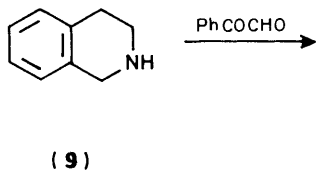
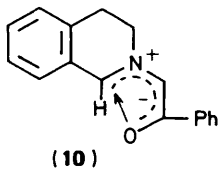
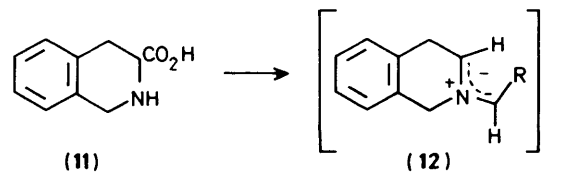


(**9**)

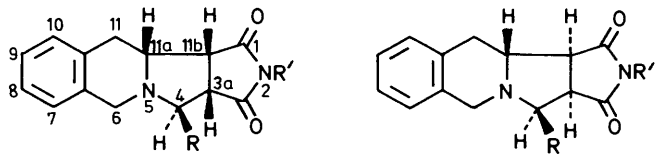


(**10**)

dipole has configuration (**4**).[16,17] The major factor producing (**4**) as the kinetic dipole is believed to be intramolecular hydrogen bonding. Similarly, our other new route to azomethine ylides involving the reaction of primary and secondary amines with carbonyl compounds containing the moiety O=C–C=X leads to regio- and stereo-specific dipole formation, *e.g.*, (**9**)→(**10**).[18] The stereospecificity in this case is proably due to

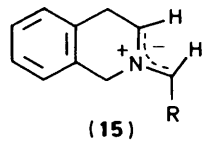


(**11**) (**12**)

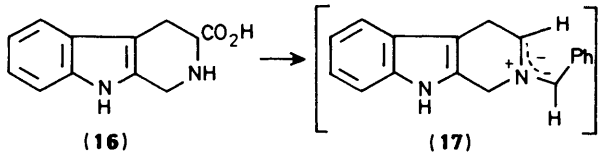


(**13**) **a**; R = R′ = Ph
b; R = Ph, R′ = Me

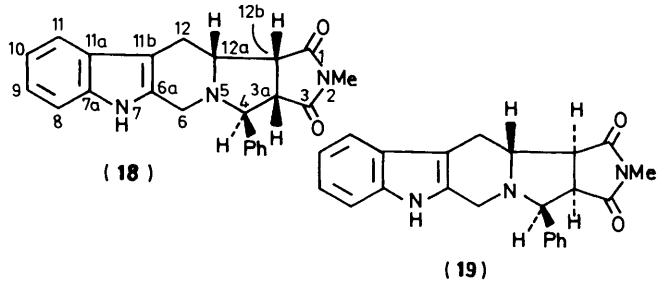
(**14**) **a**; R = R′ = Ph
b; R = Ph, R′ = Me



(**15**)



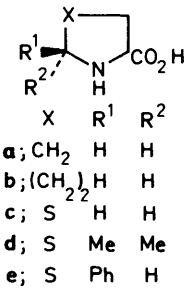
(**16**) (**17**)



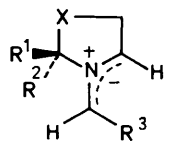
(**18**) (**19**)

favourable intramolecular dipole interation [(**10**), arrow]. In contrast to the latter two cases the production of dipoles by Scheme 3 would appear to have no obvious features likely to determine the stereochemistry of the azomethine ylide or to promote retention of stereochemistry integrity in the azomethine ylide once formed. However, since the stereochemistry of azomethine ylides produced by the Strecker Degradation will be important in synthetic applications of this process we undertook a detailed study of this aspect of the reaction. *N*-Methyl- and *N*-phenyl-maleimide were selected as the dipolarophiles since previous studies of azomethine ylides produced by the 1,2-prototropy route showed these dipolarophiles trap the kinetically formed dipole and prevent dipole stereomutation.[17]

When tetrahydroisoquinoline-3-carboxylic acid (**11**), benzaldehyde, and *N*-methyl- or *N*-phenyl-maleimide are heated at 120 °C in DMF over 1.5 h, the sparingly soluble (**11**) slowly dissolves with evolution of carbon dioxide. Removal of the solvent gave a crude product whose ^{1}H n.m.r. spectrum, in the case of the *N*-phenylmaleimide adduct, showed it to comprise an approximately 1:1 mixture of compounds (**13a**) and (**14a**). Four new stereocentres are created in the cycloaddition but both products are derived from the same configuration (**12**; R = Ph) of the intermediate azomethine ylide. Dipole configuration (**12**) is termed '*anti*' whilst the alternative dipole configuration (**15**) is termed '*syn*'. The stereochemical assignments in this



	X	R^1	R^2
(20) a;	CH_2	H	H
b;	$(CH_2)_2$	H	H
c;	S	H	H
d;	S	Me	Me
e;	S	Ph	H



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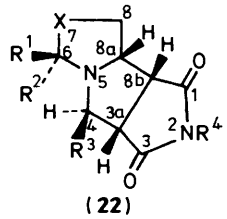

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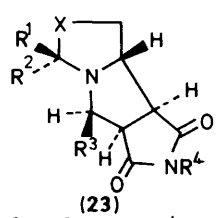

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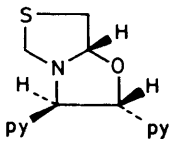
	X	R^1	R^2	R^3	R^4
a;	CH	H	H	Ph	Ph
b;	$(CH_2)_2$	H	H	Ph	Me
c;	S	H	H	Ph	Ph
d;	S	Me	Me	2-pyridyl	Me
e;	S	Ph	H	Ph	Ph



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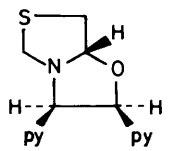
py = 2-pyridyl



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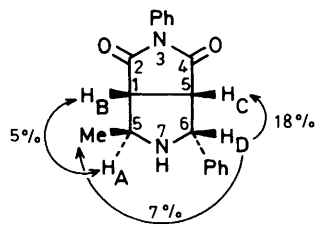
py = 2-pyridyl



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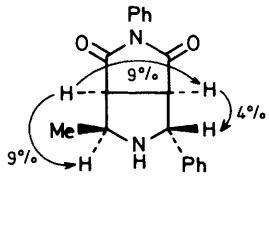

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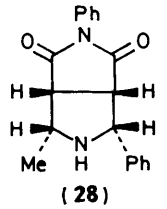

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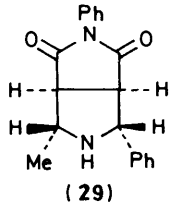

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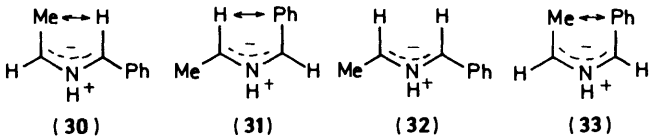


(30) (31) (32) (33)

Table 1. N.O.e. and coupling constant data ($CDCl_3$) for (**13a**) and (**14a**)

Compound		N.O.e. (%) 3a-H	4-H	11a-H	11b-H	Coupling constant (Hz)
(**13a**)	3a-H		5		10	$J_{3a,4}$ 1
	4a-H	5				
	11a-H[a]				13	$J_{3a,11b}$ 8
	11b-H[a]	11		11		$J_{11a,11b}$ 9
(**14a**)	3a-H		10		7	$J_{3a,4}$ 9
	4-H	18				
	11b-H	11		4		$J_{3a,11b}$ 8
						$J_{11a,11b}$ 0

[a] Spectrum determined in [$^2H_5$]pyridine.

paper are based on a variety of n.m.r. techniques. 2D-COSY was used to assist with assignment of the protons whilst n.O.e. difference spectroscopy was used extensively to assign relative stereochemistry which was corroborated wherever possible by coupling constant data. Typical data is illustrated in Table 1 for compounds (**13a**) and (**14a**).

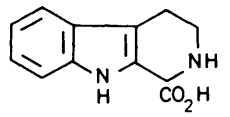
The product from the reaction of (**11**), benzaldehyde, and *N*-methylmaleimide consisted of an approximately 1:1 mixture of (**13b**) and (**14b**) together with a trace amount (*ca.* 2%) of a third isomer arising from the *syn*-dipole (**15**; R = Ph). The *anti-endo*-(**13**) and *anti-exo*-(**14**)-cycloadducts are thus formed in approximately equal amounts in contrast to the situation when dipoles (**4a** and **b**) generated by 1,2-prototropy react with *N*-substituted maleimides. In these latter cases only *endo*-adducts are obtained.[17] An analogous result to (**11**) was obtained with tetrahydro-β-carboline-3-carboxylic acid (**16**) which similarly (DMF, 120 °C, 5 h) gives an approximately 1:1 mixture (59%) of (**18**) and (**19**) *via* the *anti*-dipole (**17**).

Proline (**20a**), pipecolinic acid (**20b**), and thiazolidine-4-carboxylic acid (**20c**) react in an analogous way to (**11**) and (**16**), *via* the *anti*-dipole (**21**; R^3 = Ph), on heating in DMF, toluene, acetonitrile, or methanol, with benzaldehyde and *N*-substituted maleimides (Table 2). The substituted thiazolidines (**20d** and **e**) give similar results (Table 2) but in the case of (**20e**), the *anti*-dipole (**21**; R^1 = R^3 = Ph, R^2 = H, X = S) undergoes a diastereofacially specific cycloaddition to the face of the dipole

Table 2. Product ratios from cycloadditions of acids (**20a**—**d**), aldehydes, and *N*-methylmaleimide

Acid	Aldehyde	Solvent	Temp. (°C)	Reaction time (h)	Yield (%)[a]	Product ratio[b] 22:23
(**20a**)	PhCHO	DMF	120	1.5	87	1.3:1[c]
(**20a**)	PyCHO[d]	MeOH	60	0.5	59	1.5:1
(**20b**)	PhCHO	DMF	120	2	71	1.1:1
(**20c**)	PhCHO	DMF	120	4	68	1.1:1[e]
(**20c**)	PhCHO	Toluene	110	12	79	1.5:1[c]
(**20d**)	PyCHO[d]	Acetonitrile	80	10	76	2:1
(**20e**)	PhCHO	Toluene	110	12	70	1.5:1[c]

[a] Isolated yield. [b] Calculated by integration of the 250 MHz ^1H n.m.r. spectrum of the crude reaction product. [c] *N*-Phenylmaleimide adducts. [d] Pyridine-2-carbaldehyde. [e] The *anti-endo*-cycloadduct stereochemistry could not be completely assigned in this case due to overlapping signals in the ^1H n.m.r. spectrum.



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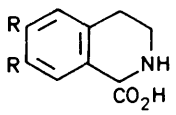
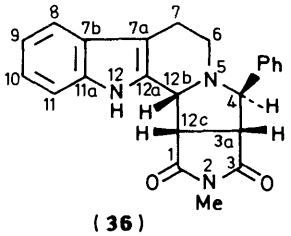


(35) a ; R = H
b ; R = OMe



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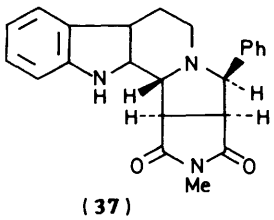

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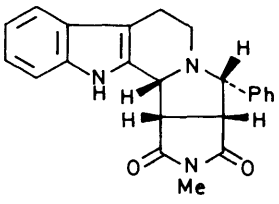

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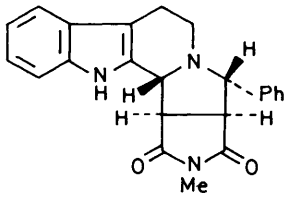

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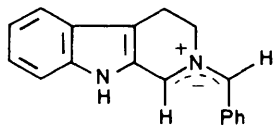

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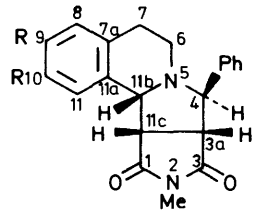
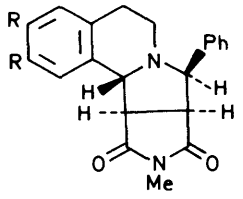


(41) a ; R = H
b ; R = OMe



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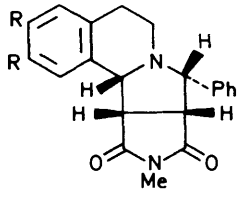

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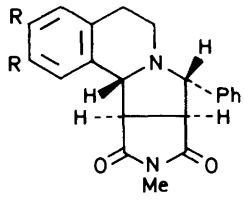

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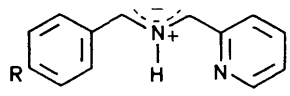


(45)

remote from the sp^3 C–Ph (R^1) group. The product consisted of a 1.5:1 mixture (70%) of *endo*-(**22e**)- and *exo*-(**23e**)-cycloadducts (Table 2). Similar results are obtained when benzaldehyde is replaced by pyridine-2-carbaldehyde (Table 2).

The thiazolidine-4-carboxylic acid (**20c**) also reacts with 2 moles of pyridine-2-carbaldehyde (acetonitrile, 80 °C, 12 h) to give a 2:1 mixture (54%) of *endo*-(**24**)- and *exo*-(**25**)-cycloadducts derived from the *anti*-dipole (**21**; $R^1 = R^2 = H$, R^3 = 2-pyridyl, X = S).

The foregoing results show that acids (**11**), (**16**), and (**20a—e**) give rise to adducts solely derived from an intermediate *anti*-dipole. However, examples were also found where the preference for the *anti*-dipole was diminished or absent. Thus alanine, benzaldehyde, and *N*-phenylmaleimide react (DMF, 153 °C, 0.75 h) to give an 11 : 5.6:1:1 mixture of isomers (**26**)—(**29**) in which the two major isomers (**26**) and (**27**) are derived from the *anti*-dipole (**30**).

The stereochemistry of (**26**)—(**29**) was assigned on the basis of n.O.e. difference spectroscopy [see (**26**) and (**27**)], coupling constants, and comparisons with related adducts.[19] These stereochemical studies indicate that (**26**) arises either from *endo*-addition to (**30**) or *exo*-addition to (**31**). Azomethine ylide (**31**) is sterically less favourable than (**30**) (Ph/H repulsion > Me/H repulsion) suggesting most, if not all, of (**26**) derives from (**30**) *via* an *endo*-transition state. Similarly, the two minor isomers (**28**) and (**29**) are derived from the *syn*-dipole (**32**) rather than the sterically congested (**33**).

The stereoselectivity of dipole formation is noticeably less in the case of cycloadditions of tetrahydro-β-carboline-1-carboxylic acid (**34**), and no dipole configuration specificity is observed in the case of tetrahydroisoquinoline-1-carboxylic acids (**35a** and **b**). The acids (**34**) and (**35a**) react appreciably faster than their corresponding 3-carboxylic acid isomers. Thus (**34**) reacts (DMF, 120 °C, 0.3 h) with benzaldehyde and *N*-methylmaleimide to give a 2.2:2:1:1.2 mixture of (**36**)—(**39**) (76%). The two major adducts, *anti-endo*-(**36**) and *anti-exo*-(**37**), are derived from the *anti*-dipole (**40**) and the two minor adducts, *syn-endo*-(**38**) and *syn-exo*-(**39**), from the *syn*-dipole. The acid (**35a**) reacts (DMF, 120 °C, 1 h) to give a 1.2:1.7:1:1.9 mixture of (**41a**)—(**44a**) and the dimethoxy analogue (**35b**) gives very similar results. Thus heating (**35b**) with benzaldehyde and *N*-methylmaleimide (DMF, 120 °C, 2 h) gives a 1.1:1.5:1:1.4 mixture (79%) of (**41b**)—(**44b**). The ratio of *anti*:*syn* dipole adducts from (**34**), (**35a**), and (**35b**) is 1.9:1, 1:1, and 1.1:1 respectively. Thus cyclic secondary amino acids in which the carboxyl group is located at a benzylic site show a sharply reduced or absence of stereoselectivity for *anti*-dipole formation.

Thus we have a gradation in stereoselectivity depending on the nature of the α-amino acid precursor of the azomethine ylide. The stereospecific *anti*-dipole formation in the case of acids (**11**), (**16**), and (**20a—e**) necessitates modification of the original simple scheme (Scheme 3)[8] for azomethine ylide formation either by involving some non-covalent configuration determining interaction or by incorporation of an intermediate capable of exerting control over dipole stereochemistry. Further studies designed to elucidate the nature of this possible intermediate together with a revised mechanism for azomethine ylide formation *via* the decarboxylative route are reported in the following paper.[19]

The cycloadducts reported in this paper whether derived from *syn*- or *anti*-dipoles show little, if any, stereoselection between *endo*- and *exo*-transition states in marked contrast to the stereospecific *endo*-cycloaddition displayed by (**4a**) and (**4b**) with maleimide dipolarophiles.[17] This suggests that steric interactions in the two transition states are fairly evenly balanced and that secondary orbital interactions between the maleimide and the single aryl group (phenyl or pyridyl) of the azomethine ylide are small or absent. This aspect of the reaction is the subject of further study. We have previously reported the effect of the *p*-substituent (R) in (**45**) on the ratio of *endo*:*exo* cycloadducts with a maleimide dipolarophile.[20]

Experimental

General spectroscopic details were as previously noted.[21] Flash chromatography employed Silica Gel 60 (Merck 9385).

General Procedure for Cycloaddition Reactions in DMF.—A mixture of carboxylic acid (0.01 mol), aldehyde (0.01 mol), and dipolarophile (0.01 mol) in DMF (50 ml) was stirred and heated at 120 °C. When evolution of carbon dioxide ceased, or in the case of sparingly soluble acids when all the acid had dissolved, the reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and washed with water (3 ×), dried (Na_2SO_4), and evaporated to dryness. Integration of the ^1H n.m.r. spectrum of the crude product gave the isomer ratio. Isomer mixtures were separated by flash chromatography.

2,3,3aα,4β,6,11,11aα,11bα- *and* 2,3,3aα,4α,6,11,11aβ,11bα-*Octahydro-2,4-diphenyl-1H-pyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-b]-*isoquinoline-1,3-dione* (**13a**) *and* (**14a**).—These were prepared (79%, combined yield) from tetrahydroisoqinoline-3-carboxylic acid, benzaldehyde, and *N*-phenylmaleimide in DMF at 120 °C for 1.5 h according to the general procedure. The crude product was separated by flash chromatography, eluting with 12:1 v/v toluene–ether to give (**13a**) (37%) and (**14a**) (42%).

Compound (**13a**). Colourless rods (ethanol), m.p. 216—218 °C (Found: C, 78.9; H, 5.9; N, 7.1. $C_{26}H_{22}N_2O_2$ requires C, 79.2; H, 5.6; N, 7.1%); $\nu_{max.}$ 1 770, 1 697 (amide), 750, 700, and 693 cm^{-1}; δ 2.80 (1 H, dd, *J* 12 and 16 Hz, 11-H), 3.16 (1 H, dd, *J* 3 and 16 Hz, 11-H), 3.31 (1 H, d, *J* 15 Hz, 6-H), 3.55 (1 H, m, 11a-H), 3.68 (1 H, dd, *J* 8 and 1 Hz, 3a-H), 3.88 (1 H, d, *J* 15 Hz, 6-H), 3.91 (1 H, t, *J* 8 Hz, 11b-H), 4.91 (1 H, br s, 4-H), and 6.88—7.54 (14 H, m, ArH); *m/z* (%) 394 (M^+, 100) and 221 (48).

Compound (**14a**). Colourless prisms (methanol), m.p. 207—209 °C (Found: C, 78.9; H, 5.7; N, 6.9); $\nu_{max.}$ 1 770, 1 700 (amide), 755, 740, 700, and 690 cm^{-1}; δ 2.92 (2 H, d, *J* 8 Hz, 11-H), 3.34 (1 H, d, *J* 8 Hz, 11b-H), 3.65 (1 H, t, *J* 8.5 Hz, 3a-H), 3.70 (1 H, d, *J* 18 Hz, 6-H), 4.20 (1 H, d, *J* 18 Hz, 6-H), 4.26 (1 H, t, *J* 8 Hz, 11a-H), 4.47 (1 H, d, *J* 9 Hz, 4-H), and 6.90—7.46 (14 H, m, ArH); *m/z* (%) 394 (M^+, 99), 221 (60), and 104 (100).

2,3,3aα,4β,6,11,11aα,11bα- *and* 2,3,3aα,4α,6,11,11aβ,11bα-*Octahydro-2-methyl-4-phenyl-1H-pyrrolo*[3′,4′:3,4]*pyrrolo*-[1,2-b]*isoquinoline-1,3-dione* (**13b**) *and* (**14b**).—Prepared (82% combined yield) from tetrahydroisoquinoline-3-carboxylic acid, benzaldehyde, and *N*-methylmaleimide as above. Purification by flash chromatography gave (**13b**) (42%) and (**14b**) (38%). A small amount (~20%) of a third isomer arising from the *syn*-dipole (**15**) was obtained as a gum and was not characterised further.

Compound (**13b**). Colourless prisms (methanol), m.p. 167—169 °C (Found: C, 75.9; H, 6.1; N, 8.5. $C_{21}H_{20}N_2O_2$ requires C, 75.9; H, 6.1; N, 8.4%); $\nu_{max.}$ 1 760, 1 695 (amide), 770, 760, 750, and 710 cm^{-1}; δ 2.67 (1 H, dd, *J* 16 and 11 Hz, 11-H), 3.04 (3 H, s, 2-Me), 3.10 (1 H, dd, *J* 4 and 16 Hz, 11-H), 3.22 (1 H, d, *J* 15 Hz, 6-H), 3.45 (1 H, m, 11a-H), 3.51 (1 H, d, *J* 7 Hz, 3a-H), 3.75 (1 H, t, *J* 8 Hz, 11b-H), 3.80 (1 H, d, *J* 15 Hz, 6-H), 4.79 (1 H, s, 4-H), and 6.89—7.44 (9 H, m, ArH); *m/z* (%) 332 (M^+, 89), 221 (28), and 104 (100).

Compound (**14b**). Colourless platelets (methanol), m.p. 167—169 °C (Found: C, 75.75; H, 6.2; N, 8.4); $\nu_{max.}$ 1 760, 1 685 (amide), 760, 750, and 700 cm^{-1}; δ 2.88 (2 H, d, *J* 8 Hz, 11-H), 2.93 (3 H, s, 2-Me), 3.17 (1 H, d, *J* 8 Hz, 11b-H), 3.52 (1 H, dd, *J* 8 and 9 Hz, 3a-H), 3.62 (1 H, d, *J* 17 Hz, 6-H), 4.15 (1 H, t, *J* 8 Hz, 11a-H), 4.15 (1 H, d, *J* 17 Hz, 6-H), 4.36 (1 H, d, *J* 9 Hz, 4-H), and 6.87—7.38 (9 H, m, ArH); *m/z* (%) 332 (M^+, 76), 221 (36), and 104 (100).

1,2,3,3aα,4β,6,7,12,12aα,12bα- *and* 1,2,3,3aα,4α,6,7,12,12aβ,-12bα-*Decahydro-2-methyl-4-phenylpyrrolo*[3′,4′:1,2]*indolizino*[5,7-b]*indole-1,3-dione* (**18**) *and* (**19**).—Prepared (59% combined yield) from tetrahydro-β-carboline-3-carboxylic acid, benzaldehyde, and *N*-methylmaleimide in DMF at 120 °C for 4.5 h. The crude product showed four spots on t.l.c. (silica, 4:1 v/v benzene–ether) with R_F 0.48, 0.33, 0.24, and 0.16 (iodoplatinate spray) only two of which (R_F 0.33 and 0.24) were cycloadducts. Separation by flash chromatography eluting with 4:1 v/v benzene–ether gave (**19**) (25%) and (**18**) (34%).

Compound (**18**). Colourless prisms (ethanol), m.p. 160—162 °C (Found: C, 74.5; H, 5.9; N, 11.1. $C_{23}H_{21}N_3O_2$ requires C, 74.4; H, 5.7; N, 11.3%); $\nu_{max.}$ 3 400 (NH), 1 770, 1 700 (amide), 760, 750, 715, and 710 cm^{-1}; δ 2.53—2.58 (1 H, dd, 12β-H), 3.05 (3 H, s, 2-Me), 3.07—3.14 (1 H, dd, 12α-H), 3.33 (1 H, d, *J* 14 Hz, 6α-H), 3.50 (1 H, dd, *J* 1 and 8 Hz, 3a-H), 3.63 (1 H, m, 12a-H), 3.73 (1 H, d, *J* 14 Hz, 6β-H), 3.74 (1 H, t, *J* 8 Hz, 12b-H), 4.70 (1 H, *J* 1 Hz, 4-H), 7.06—7.47 (9 H, m, ArH), and 7.66 (1 H, br s, 7-H); ^1H NOEDSY: irradiation of 3a-H caused enhancement of 4-H (3%), 12b-H (5), and ArH (6); irradiation of 4-H caused enhancement of 3a-H (3), ArH (9), and 6β-H (2); irradiation of 12β-H caused enhancement of 4-H (1.3), 12a-H (2), and 12α-H(23); irradiation of 12a-H caused enhancement of 12α-H(4) and ArH (8) but no enhancement of 4-H and 12β-H; *m/z* (%) 371 (M^+, 10) and 143 (100).

Compound (**19**). Colourless prisms (ethanol), m.p. 276—279 °C (Found: C, 74.5; H, 5.8; N, 11.5); $\nu_{max.}$ 3 320 (NH), 1 770, 1 690 (amide), 760, 750, and 705 cm^{-1}; δ 2.80—3.04 (2 H, m, 12α- and 12β-H), 2.93 (3 H, s, 2-Me), 3.24 (1 H, d, *J* 8 Hz, 12b-H), 3.53 (1 H, t, *J* 8.5 Hz, 3a-H), 3.60 (1 H, d, *J* 17 Hz, 6α-H), 4.16 (1 H, d, *J* 17 Hz, 6β-H), 4.18 (1 H, dd, *J* 6 and 11 Hz, 12a-H), 4.36 (1 H, d, *J* 9 Hz, 4-H), 7.09—7.59 (9 H, m, ArH), and 7.62 (1 H, br s, 7-H); ^1H NOEDSY: irradiation of 3a-H caused enhancement of 4-H (9%) and 12b-H (5); irradiation of 4-H caused enhancement of 3a-H (11), 6α-H (2), and 12β-H (4); irradiation of 12b-H caused enhancement of 3a-H (7) and 12a-H (4); *m/z* (%) 371 (M^+, 7) and 143 (100).

1,2,3,3aα,4β,6,7,8,8aα,8bα- *and* 1,2,3,3aα,4α,6,7,8,8aβ,8bα-*Decahydro-2,4-diphenylpyrrolo*[3,4-a]*pyrrolizine-1,3-dione* (**22a**) *and* (**23a**).—Prepared (87% combined yield) from proline, benzaldehyde, and *N*-phenylmaleimide in DMF at 120 °C for 1.5 h according to the general method. Separation by flash chromatography afforded pure samples of (**22a**) (36%) and (**23a**) (35%) together with mixed fractions (16%).

Compound (**22a**). Colourless prisms (ethanol–light petroleum), m.p. 101—102 °C (Found: C, 76.1; H, 6.3; N, 8.7. $C_{21}H_{20}N_2O_2$ requires C, 75.9; H, 6.1; N, 8.4%); $\nu_{max.}$ 1 770, 1 700 (amide), 760, and 700 cm^{-1}; δ 2.01 (4 H, m, 7- and 8-H), 2.75 (1 H, m, 6β-H), 3.11 (1 H, m, 6α-H), 3.55 (1 H, dd, *J* 5.5 and 9 Hz, 3a-H), 3.73 (1 H, t, *J* 9 Hz, 8b-H), 4.04 (1 H, m, 8a-H), 4.33 (1 H, d, *J* 5.5 Hz, 4-H), and 7.19—7.54 (10 H, m, ArH); ^1H NOEDSY: irradiation of 4-H caused enhancement of 3a-H (1.6%), 6β-H (6) and ArH (11); irradiation of 8a-H caused enhancement of 8b-H (9), 6α-H (2), ArH (8), and 8-H (7); irradiation of 3a-H caused enhancement of 4-H (2) and ArH (6); *m/z* (%) 332 (M^+, 29) and 159 (100).

Compound (**23a**). Colourless needles (ethanol), m.p. 195—198 °C (Found: C, 75.7; H, 6.3; N, 8.4); $\nu_{max.}$ 1 770, 1 705 (amide), 760, 705, and 695 cm^{-1}; δ 1.96 (4 H, m, 7- and 8-H), 2.77 (1 H, m, 6α-H), 2.94 (1 H, m, 6β-H), 3.45 (1 H, dd, *J* 1 and 8 Hz, 8b-H), 3.68 (1 H, t, *J* 8.5 Hz, 3a-H), 3.95 (1 H, br t, *J* 8 Hz, 8a-H), 4.22 (1 H, d, *J* 9 Hz, 4-H), and 7.11—7.50 (10 H, m, ArH); ^1H NOEDSY: irradiation of 4-H caused enhancement of 3a-H (16%), 6α-H (3), and ArH (12); irradiation of 3a-H caused enhancement of 4-H (12) and 8b-H (9); irradiation of 8a-H caused enhancement of 8b-H (5), 8-H (6), 6β-H (1.4), and ArH (4); *m/z* (%) 332 (M^+, 23) and 159 (100).

1,2,3,3aα,4β,6,7,8,8aα,8bα- *and* 1,2,3,3aα,4α,6,7,8,8aβ,8bα-*Decahydro-2-phenyl-4-(2-pyridyl)pyrrolo*[3,4-a]*pyrrolizine-1,3-dione* (**22a**; R^3 = 2-*pyridyl*) *and* (**23a**; R^3 = 2-*pyridyl*).—A mixture of pyridine-2-carbaldehyde (550 mg), proline (600 mg),

Table 3. ^{1}H NOEDSY results for (**22a**) and (**23a**)

Proton irradiated	Proton observed	Enhancement (**22a**) R^3 = 2-pyridyl	Enhancement (**23a**) R^3 = 2-pyridyl
4-H	3a-H	5.5	13
	8a-H	1.5	
	6-H	5	5
	PyH	8	
3a-H	4-H	4	10
	8b-H	10	29
8b-H	3a-H	17	11
	8a-H	14.5	6
8a-H	8b-H	14.5	
	8-H	5	
	4-H	1[a]	

[a] The signals for 3a-H and 8a-H are very close and this very small enhancement may have arisen from the 3a-H.

and *N*-phenylmaleimide (900 mg) in methanol (70 ml) was boiled under reflux for 0.5 h. The solvent was then evaporated off to leave a brown viscous oil (1.6 g) the ^{1}H n.m.r. spectrum of which showed it to consist of a 1.47:1 mixture of (**22a**; R^3 = 2-pyridyl) and (**23a**; R^3 = 2-pyridyl). Purification by preparative t.l.c. afforded pure samples of both isomers (59% combined yield).

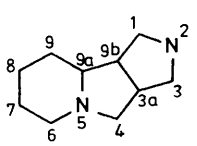
Compound (**22a**; R^3 = 2-pyridyl). Pale yellow viscous oil (600 mg); δ 2.05 (2 × 2 H, 2 × m), 3.28 and 2.75 (2 × 1 H, 2 × m), 3.67 (1 H, t, 8b-H, *J* 9.0 Hz), 4.08 (1 H, m, 8a-H), 4.22 (1 H, dd, 3a-H, *J* 8.8 Hz), 4.73 (1 H, d, 4β-H, *J* 3.1 Hz), 7.47 (8 H, m, ArH + PyH), and 8.60 (1 H, dd, PyH).

Compound (**23a**; R^3 = 2-pyridyl). Colourless needles (400 mg) from benzene, m.p. 170 °C (Found: C, 71.85; H, 5.65; N, 12.65. $C_{20}H_{19}N_3O_2$ requires C, 72.05; H, 5.75; N, 12.60%); δ 2.00 (2 × 2 H, m), 2.77 and 3.04 (2 × 1 H, 2 × m), 3.46 (1 H, dd, 8b-H, *J* 1.8 Hz), 4.00 (1 H, m, 8a-H), 3.91 (1 H, t, 3a-H, *J* 8.5 Hz), 4.42 (1 H, d, 4α-H, *J* 8.6 Hz), 7.43 (8 H, m, ArH + PyH), and 8.57 (1 H, dd, PyH); *m/z* (%) 255 (100). ^{1}H NOESDY results for (**22a**) and (**23a**) are in Table 3.

2,3,3aα,4β,6,7,8,9aα,9bα- *and* 2,3,3aα,4α,6,7,8,9aβ,9bα- *Decahydro-2-methyl-4-phenyl-*1H*-pyrrolo*[3,4-a]*indolizine-*1,3*-dione* (**22b**) *and* (**23b**).*—Prepared (72% combined yield) from pipecolinic acid, benzaldehyde, and *N*-methylmaleimide in DMF at 120 °C for 2 h. The two isomers were separated by flash chromatography eluting with 1:2 v/v ethyl acetate–light petroleum to give (**22b**) (41%), (**23b**), (30%), and a mixed fraction (1%).

Compound (**22b**). Colourless prisms (benzene), m.p. 172—174 °C (Found: C, 71.5; H, 7.15; N, 9.6. $C_{17}H_{20}N_2O_2$ requires C, 71.8; H, 7.1; N, 9.85%); $\nu_{max.}$ 1 765, 1 685 (amide), 765, and 710 cm^{-1}; δ 1.19 (4 H, m 7- and 8-H), 1.60 (1 H, m, 9-H), 1.71 (1 H, br d, 6-H), 2.01 (1 H, br d, 6-H), 2.79 (2 H, m, 9- and 9a-H), 3.04 (3 H, s, 2-Me), 3.38 (1 H, d, *J* 8 Hz, 3a-H), 3.46 (1 H, t, *J* 8 Hz, 9b-H), 4.57 (1 H, s, 4-H), and 7.09—7.41 (5 H, m, ArH); *m/z* (%) 284 (M^+, 100) and 173 (70); stereochemistry assigned by comparison with (**13b**).

Compound (**23b**). Colourless rods (benzene), m.p. 157—160 °C (Found: C, 71.5; H, 7.3; N, 9.9); $\nu_{max.}$ 1 760, 1 690 (amide), 760, and 710 cm^{-1}; δ 1.49 (6 H, m, 7-, 8-, and 9-H), 2.74 (2 H, m, 6-H), 2.87 (3 H, s, 2-Me), 2.91 (1 H, d, *J* 8 Hz, 9b-H), 3.44 (1 H, t, *J* 8.4 Hz, 3a-H), 3.78 (1 H, t, *J* 7 Hz, 9a-H), 4.60 (1 H, d, *J* 9 Hz, 4-H), and 7.19—7.37 (5 H, m, ArH); *m/z* (%) 284 (M^+, 100) and 173 (81); stereochemistry assigned by comparison with (**14b**).

* 

2,3,3a,4,6,7,8,9,9a,9b-Decahydro-1*H*-pyrrolo[3,4-*a*]indolizine skeleton.

1,2,3,3aα,4β,8,8aα,8bα- *and* 1,2,3,3aα,4α,8,8aβ,8bα-*Octahydro-2-methyl-4-phenylpyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-c]*thiazole-*1,3*-dione* (**22c**) *and* (**23c**).—Prepared from thiazolidine-4-carboxylic acid, benzaldehyde, and *N*-methylmaleimide according to the general procedure. Heating was continued for 4 h. The two isomers were separated by flash chromatography eluting with 4:1 v/v toluene–ether to give (**22c**) (37%) and (**23c**) (31%).

Compound (**22c**). Colourless prisms (benzene), m.p. 195—197 °C (Found: C, 62.6; H, 5.5; N, 9.5; S, 10.8. $C_{15}H_{16}N_2OS$ requires C, 62.5; H, 5.6; N, 9.7; S, 11.1%); $\nu_{max.}$ 1 765, 1 690 (amide), 780, 755, 720, and 705 cm^{-1}; δ 2.51 (1 H, dd, *J* 10 and 11 Hz, 8β-H), 2.99 (3 H, s, 2-Me), 3.12 (1 H, dd, *J* 7 and 11 Hz, 8α-H), 3.35 (1 H, dd, *J* 8 and 9 Hz, 3a-H), 3.89 (3 H, m, 4-, 6β-, and 8b-H), 4.03 (1 H, dt, *J* 7, 7, and 10 Hz, 8a-H), 4.18 (1 H, d, *J* 10 Hz, 6α-H), and 7.29—7.51 (5 H, m, ArH); ^{1}H NOEDSY: irradiation of 3a-H caused enhancement of 4- and 8b-H together (6%) and Ar–H (2.3); irradiation of 8α-H caused enhancement of 8β-(H (19) and 8a-H (6); irradiation of 8β-H caused enhancement of 8α-H (17), 8a-H (1), and 4-H, 6β- and 8b-H together (5); irradiation of 8a-H caused enhancement of 8α-H (4) and 8β-H (19); *m/z* (%) 288 (M^+, 100).

Compound (**23c**). Colourless prisms (benzene), m.p. 198—200 °C (Found: C, 62.3; H, 5.6; N, 9.6; S, 11.4); $\nu_{max.}$ 1 765, 1 690 (amide), 760, and 700 cm^{-1}; δ 2.80 (1 H, t, *J* 10 Hz, 8α-H), 2.92 (3 H, s, 2-Me), 3.30 (1 H, dd, *J* 7 and 10 Hz, 8β-H), 3.36 (1 H, d, *J* 8 Hz, 8b-H), 3.54 (1 H, dd, *J* 8 and 9 Hz, 3a-H), 3.92 (1 H, d, *J* 10 Hz, 6α-H), 4.01 (1 H, dd, *J* 7 and 10 Hz, 8a-H), 4.21 (1 H, d, *J* 9 Hz, 4-H), 4.23 (1 H, d, *J* 10 Hz, 6β-H), and 7.24—7.49 (5 H, m, ArH); ^{1}H NOEDSY: irradiation of 3a-H caused enhancement of 4-H (5%); irradiation of 8α-H caused enhancement of 4-H (3), 8a-H (1), 8b-H (4), and 8β-H (17); irradiation of 8a-H caused enhancement of 8β-H (4) and 8b-H (2); *m/z* (%) 288 (M^+, 100).

1,2,3,3aα,4β,8,8aα,8bα- *and* 1,2,3,3aα,4α,8,8aβ,8bα-*Octahydro-2,6,6-trimethyl-*4-(2*-pyridyl*)*pyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-c]-*thiazole-*1,3*-dione* (**22d**) *and* (**23d**).—A mixture of 2,2-dimethylthiazolidine-4-carboxylic (1.0 g, 6.2 mmol), pyridine-2-carbaldehyde (670 mg, 6.2 mmol), and *N*-methylmaleimide (689 mg, 6.2 mmol) in acetonitrile (15 ml) was stirred and boiled under reflux for 10 h. The mixture was then filtered to remove unchanged thiazolidinecarboxylic acid (60 mg) and the filtrate evaporated to dryness under reduced pressure to leave a foam. This was purified by preparative t.l.c. (silica) eluting with 19:1 v/v chloroform–methanol to afford (**22d**) (940 mg) and (**23d**) (470 mg), to give a combined yield of 76%.

Compound (**22d**). Colourless cubes from methanol, m.p. 145 °C (Found: C, 60.50; H, 6.15; N, 13.40; S, 10.05. $C_{16}H_{19}N_3O_2S$ requires C, 60.55; H, 6.00; N, 13.25; S, 10.10%); δ 1.12 (3 H, s, Me), 1.55 (3 H, s, Me), 2.73 (1 H, dd, 8β-H, *J* 9.2 and 11.0 Hz), 2.94 (3 H, s, NMe), 3.15 (1 H, dd, 8α-H, *J* 7.0 and 11.0 Hz), 3.50 (1 H, dd, 3a-H, *J* 6.75 and 9.5 Hz), 3.83 (1 H, dd, 8b-H, *J* 8.4 and 9.5 Hz), 4.39 (1 H, d, 4β-H, *J* 6.75 Hz), 4.51 (1 H, dd, 8a-H, *J* 8.4 and 15.4 Hz), 7.87 (3 H, m, PyH), and 8.60 (1 H, m, PyH); *m/z* (%) 317 (M^+, 32), 302 (100), 284 (36), 243 (12), 145 (12), 132 (12), 127 (15), 113 (33), and 93 (15).

Compound (**23d**). Colourless prisms from methanol, m.p. 236—238 °C; δ 1.63 and 2.89 (2 × 3 H, 2 × s, Me), 2.97 (1 H, t, 8β-H, *J* 10.2 Hz), 3.33 (1 H, d, 8b-H, *J* 8.0 Hz), 3.38 (1 H, dd, 8α-H, *J* 7.3 and 10.2 Hz), 3.78 (1 H, dd, 3a-H, *J* 8.0 and 10.0 Hz), 4.60 (1 H, dd, 8a-H, *J* 7.3 and 9.4 Hz), 4.66 (1 H, d, 4α-H, *J* 10.0 Hz), 7.85 (3 H, m, PyH), and 8.59 (1 H, m, PyH).

1,2,3,3aα,4β,8,8aα,8bα- *and* 1,2,3,3aα,4α,8,8aβ,8bα-*Octahydro-2,4,6α-triphenylpyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-c]*thiazole*-1,3-*dione* (**22e**) *and* (**23e**).—A mixture of 2-phenylthiazolidine-4-carboxylic acid (500 mg, 2.4 mmol), *N*-methylmaleimide (430 mg, 2.5 mmol), and benzaldehyde (270 mg, 2.55 mmol) in toluene (20 ml) was stirred and boiled under reflux for 12 h. The solvent was then evaporated off under reduced pressure to leave a reddish solid (1.06 g), the n.m.r. spectrum ($CDCl_3$) of which showed it to contain a 1.5:1 mixture of (**22e**) and (**23e**). Purification by preparative t.l.c. afforded (**22e**) (450 mg) and (**23e**) (300 mg) giving a combined yield of 70%.

Compound (**22e**). Colourless needles from methanol, m.p. 166 °C (Found: C, 73.55; H, 5.45; N, 6.75. $C_{26}H_{22}N_2O_2S$ requires C, 73.25; H, 5.15; N, 6.55%); δ 2.99 (1 H, t, 8β-H, *J* 10 Hz), 3.32 (1 H, dd, 8α-H, *J* 7.1 and 10.0 Hz), 3.49 (1 H, dd, 3a-H, *J* 7.9 and 9.7 Hz), 3.92 (1 H, dd, 8b-H, *J* 8.1 and 9.7 Hz), 4.25 (1 H, d, 4β-H, *J* 7.9 Hz), 4.28 (1 H, m, 8a-H), 5.42 (1 H, s, 6β-H), and 7.36 (15 H, m, ArH); *m/z* (%) 426 (M^+, 100), 394 (18), 393 (64), 380 (11), 173 (26), 162 (12), 158 (19), 131 (14), 128 (14), 115 (12), 104 (16), and 91 (29).

Compound (**23e**). Colourless prisms from methanol, m.p. 163—165 °C; δ 3.00 (1 H, t, 6β-H, *J* 10 Hz), 3.43 (1 H, dd, 8α-H, *J* 7.3 and 10 Hz), 3.53 (1 H, d, 8bβ-H, *J* 8.0 Hz), 3.71 (1 H, dd, 3aβ-H, *J* 9.4 and 8.0 Hz), 4.41 (1 H, dd, 8aα-H, *J* 7.3 and 10.0 Hz), 4.52 (1 H, d, 4β-H, *J* 9.4 Hz), 5.50 (1 H, s, 6β-H), and 7.36 (15 H, m, ArH); *m/z* (%) 426 (M^+, 100), 393 (57), 266 (45) 246 (12), 158 (13), 128 (15), 119 (68), 112 (12), 104 (20), and 91 (34).

7α,8β- *and* 7β,8β-*Di*(2-*pyridyl*)-6-*oxa*-3-*thia*-1-*azabicyclo*-[3.3.0]*octane* (**24**) *and* (**25**).—A mixture of thiazolidine-4-carboxylic acid (2.0 g, 0.015 mol) and pyridine-2-carbaldehyde (3.2 g, 0.03 mol) in acetonitrile (30 ml) was stirred and boiled under reflux for 12 h. The solution was then allowed to cool to room temperature and unchanged thiazolidinecarboxylic acid removed by filtration. The filtrate was evaporated under reduced pressure to leave a brown solid, the ^1H n.m.r. spectrum ($CDCl_3$) of which showed it to contain a 2:1 mixture of (**24**) and (**25**). The crude material was purified by preparative t.l.c. to afford (**24**) (1.55 g) and (**25**) (770 mg) in a combined yield of 54%.

Compound (**24**). Colourless plates from light petroleum (40—60 °C)–ether, m.p. 84 °C (Found: C, 63.45; H, 5.30; N, 14.75; S, 11.30. $C_{15}H_{15}N_3OS$ requires C, 63.15; H, 5.25; N, 14.75; S, 11.25%); δ 3.20 (1 H, dd, 4β-H, *J* 4.5 and 12.0 Hz), 3.34 (1 H, dd, 4α-H, *J* 1.0 and 12 Hz), 4.02 (1 H, d, 2α-H, *J* 10.9 Hz), 4.17 (1 H, d, 2β-H), 4.35 (1 H, d, 8-H, *J* 8.7 Hz), 5.20 (1 H, d, 7-H), 5.60 (1 H, dd, 5-H, *J* 1.0 and 4.5 Hz), 7.44 (6 H, m, PyH), 8.47 (1 H, m, PyH), and 8.60 (1 H, m, PyH); *m/z* (%) 258 (M^+, 11), 252 (7), 238 (27), 224 (22), 210 (22), 199 (20), 183 (92), 181 (100), 169 (11), 154 (10), 132 (45), 131 (42), 120 (14), 104 (22), 93 (34), 84 (13), and 78 (50).

Compound (**25**). Colourless cubes from light petroleum (40—60 °C)–ether, m.p. 74—76 °C; δ 3.27 (2 H, m, 4-H), 4.08 (2 H, dd, 2α- + 2β-H, *J* 0.9 and 11.1 Hz), 4.94 (1 H, d, *J* 7.4 Hz), 5.73 (1 H, d, 7α-H, *J* 7.4 Hz), 6.02 (1 H, dd, *J* 2.5 and 4.4 Hz), 7.34 (6 H, m, PyH), 8.32 (1 H, m, PyH), and 8.37 (1 H, m, PyH).

8-*Methyl*-2,4-*dioxo*-3,6-*diphenyl*-3,7-*diazabicyclo*[3.3.0]*octane tane* (**26**)—(**29**).—Benzaldehyde (1.06 g) was added to a boiling mixture of alanine (900 mg) and *N*-phenylmaleimide (1.73 g) in DMF (40 ml). Boiling under reflux was continued until all the alanine had completely dissolved (45 min). The solvent was then removed under reduced pressure to leave a yellow brown viscous oil (2.5 g) which consisted of an 11:5.6:1:1 mixture (by 400 MHz n.m.r.) of stereoisomers (**26**)—(**29**).

Trituration of the crude product with ether precipitated the major product (**26**) which crystallised from chloroform–ether as colourless needles, m.p. 147—148 °C (Found: C, 74.60; H, 5.75; N, 9.15. $C_{19}H_{18}N_2O_2$ requires C, 74.50; H, 5.90; N, 9.15%); δ 1.39 (3 H, d, Me), 3.18 (1 H, dd, H_B, J_{AB} 1 Hz, J_{BC} 7.8 Hz), 3.58 (1 H, t, H_C), 4.23 (1 H, q, H_A), 4.93 (1 H, d, H_D, J_{CD} 8.8 Hz), and 7.29 (10 H, m, ArH).

A small sample (**27**) was obtained by preparative t.l.c. whilst (**28**) could not be separated from (**29**).

Compound (**27**), δ 1.39 (3 H, d, Me), 3.38 (1 H, t, H_B, J_{AB} 8 Hz), 3.68 (1 H, dd, H_C, J_{BC} 8 Hz), 3.75 (1 H, m, H_A), 4.94 (1 H, d, H_D, J_{CD} 1 Hz), and 7.2 (10 H, m, ArH).

Compounds (**28**) and (**29**), δ 1.5 (2 × 3 H, 2 × d, 2 × Me), 3.25 and 3.11 (2 × 1 H, t and q, 2 × H_B), 3.46 (4 H, m, 2 × H_A and 2 × H_C), 4.54 and 4.42 (2 × 1 H, 2 × d, 2 × H_D, J_{CD} 7.0 and 8.5 Hz), and 7.25 (m, ArH).

1,2,3,3a,4,6,7,12,12b,12c-*Decahydro*-2-*methyl*-4-*phenyl-pyrrolo*[3′,4′:1,2]*indolizino*[8,7-b]*indole*-1,3-*dione* (**36**)—(**39**).—Prepared from tetrahydro-β-carboline-1-carboxylic acid, benzaldehyde, and *N*-methylmaleimide by the general method. Heating of the DMF solution was continued for 0.75 h. The mixture of isomers was separated by flash chromatography with gradient elution from 9:1 v/v toluene–ether to 3:1 v/v toluene–ether. Ethyl acetate was used to elute the final isomer. By these means was obtained (**39**) (412 mg, 11%), (**36**) (989 mg, 27%), (**37**) (979 mg, 26%), and (**38**) (420 mg, 12%).

1,2,3,3aα,4β,6,7,12,12bα,12cα-*Decahydro isomer* (**36**). Colourless prisms (ethanol), m.p. 153—154 °C (Found: C, 74.2; H, 5.9; N, 11.05. $C_{23}H_{21}N_3O_2$ requires C, 74.4; H, 5.7; N, 11.3%); $\nu_{max.}$ 3 410 (NH), 1 765, 1 690 (amide), 755, 750, 740, and 710 cm^{-1}; δ 2.36—3.06 (4 H, m, 6- and 7-H), 2.84 (3 H, s, 2-Me), 3.40 (1 H, dd, *J* 7 and 9 Hz, 3a-H), 3.98 (1 H, t, *J* 9 Hz, 12c-H), 4.28 (1 H, d, *J* 7 Hz, 4-H), 5.15 (1 H, d, *J* 9 Hz, 12b-H), 7.07—7.52 (9 H, m, ArH), and 8.45 (1 H, s, 12-H); ^1H NOEDSY: irradiation of 3a-H caused enhancement of 12c-H (12%) and Ar-H (7.4%); irradiation of 12-H caused enhancement of 12b-H (4); irradiation of 12b-H caused enhancement of 12c-H (19) and 12-H (3); irradiation of 12c-H caused enhancement of 3a-H (18) and 12b-H (19); *m/z* (%) 371 (M^+, 100) and 260 (M − 111, 62).

1,2,3,3aα,4α,6,7,12,12bβ,12cα-*Decahydro isomer* (**37**). Colourless rods (ethanol), m.p. 260—262 °C (Found: C, 74.1; H, 5.8; N, 11.0); $\nu_{max.}$ 3 330 (NH), 1 765, 1 680 (amide), 775, 750, 740, 730, 715, 705, and 695 cm^{-1}; δ 2.44—3.12 (4 H, m, 6- and 7-H), 3.00 (3 H, s, 2-Me), 3.35 (1 H, t, *J* 8.5 Hz, 4-H), 3.52 (1 H, d, *J* 8 Hz, 12c-H), 4.45 (1 H, d, *J* 9 Hz, 3a-H), 5.12 (1 H, s, 12b-H), 7.11—7.51 (9 H, m, ArH), 8.44 (1 H, s, 12-H); ^1H NOEDSY: irradiation of 12c-H caused enhancement of 12b-H (6%) and 12-H (6); irradiation of 4-H caused enhancement of 3a-H (10) and 12c-H (12); irradiation of 12-H caused enhancement of 12b-H (4) and 12c-H (10); irradiation of 3a-H caused enhancement of 4-H (15); irradiation of 12b-H caused enhancement of 3a-H (2) and 12c-H (4); *m/z* (%) 371 (M^+, 100) and 260 (84).

1,2,3,3aα,4α,6,7,12,12bα,12cα-*Decahydro isomer* (**38**). Colourless rods (ethanol), m.p. 249—252 °C (Found: C, 74.6; H, 5.95; N, 11.1); $\nu_{max.}$ 3 340 (NH), 1 770, 1 690 (amide), 775, 760, 745, and 710 cm^{-1}; δ 2.30—2.37 (1 H, m, 6α-H), 2.75 (1 H, m, 7α-H), 2.82 (3 H, s, 2-Me), 2.95 (1 H, m, 7β-H), 3.20 (1 H, dd, 6β-H), 3.50 (1 H, t, *J* 8 Hz, 3a-H), 3.59 (1 H, t, *J* 7.5 Hz, 12c-H), 3.91 (1 H, d, *J* 8 Hz, 4-H), 3.92 (1 H, d, *J* 7 Hz, 12b-H), 7.09—7.51 (9 H, m, ArH), and 8.48 (1 H, br s, 12-H); ^1H NOEDSY: irradiation of 3a-H caused enhancement of 4- and 12b-H together (9%); irradiation of 12c-H caused enhancement of 12-H (2), 4- and 12b-H together (6.5); *m/z* (%) 371 (M^+, 75), 367 (100) and 260 (56).

1,2,3,3aα,4β,6,7,12,12bβ,12aα-*Decahydro isomer* (**39**). Colourless needles (ethanol), m.p. 239—242 °C (Found: C, 74.3; H, 6.0; N, 11.4); $\nu_{max.}$ 3 420 (NH), 1 760, 1 690 (amide), 750, and 710 cm^{-1}; δ 2.43 (1 H, m, 6β-H), 2.75 (1 H, m, 7β-H), 2.94 (1 H, m, 7α-H), 3.08 (3 H, s, 2-Me), 3.10 (1 H, m, 6α-H), 3.32 (1 H, dd, *J*

6 and 9 Hz, 3a-H), 3.41 (1 H, t, *J* 9 Hz, 11c-H), 3.56 (1 H, dt, *J* 2.2 and 9 Hz, 12b-H), 3.79 (1 H, d, *J* 6 Hz, 4-H), 7.10—7.54 (9 H, m, ArH), and 8.59 (1 H, br s, 12-H); ^{1}H NOEDSY: irradiation of 3a-H caused enhancement of 4-H (1.7%); irradiation of 4-H caused enhancement of ArH (6), 3a-H (0.6), and 12b-H (5); irradiation of 6α-H caused enhancement of 4-H (3) and 12b-H (5); irradiation of 12b-H caused enhancement of 12-H (1) and 4-H (7); *m/z* (%) 371 (M^+, 100) and 260 (50).

2,3,3a,4,6,7,11b,11c-*Octahydro*-2-*methyl*-4-*phenyl*-1H-*pyrrolo*[3′,4′:3,4]*pyrrolo*[2,1-a]*isoquinoline*-1,3-*dione* (**41a**)—(**44a**).—Prepared by the general procedure from tetrahydroisoquinoline-1-carboxylic acid, benzaldehyde, and *N*-methylmaleimide in DMF at 120 °C for 1 h. The crude mixture of isomers was separated by flash chromatography eluting with 9:1 v/v toluene–ether to give (**44a**) (22%), a mixture of (**41a**) and (**42a**) (48%), and (**43a**) (13%). Fractional crystallisation from methanol afforded a pure sample of (**42a**) and further flash chromatography of the mother liquors from the fractional crystallisation afforded pure (**41a**). The stereochemistry of the cycloadducts was assigned by comparisons of their n.m.r. spectra with those of the dimethoxy analogues (**41b**)—(**44b**) (below).

2,3,3aα,4β,6,7,11bα,11cα-*Octahydro isomer* (**41a**). Colourless prisms (ethanol), m.p. 113—115 °C (Found: C, 75.7; H, 6.1; N, 8.6. $C_{21}H_{20}N_2O_2$ requires C, 75.9; H, 6.1; N, 8.4%); $\nu_{max.}$ 1 770, 1 695 (amide), 760, 755, 730, and 710 cm^{-1}; δ 2.34 (1 H, m, 7-H), 2.82 (3 H, m, 6- and 7-H), 2.89 (3 H, s, 2-Me), 3.62 (1 H, d, *J* 8 Hz, 3a-H), 3.81 (1 H, t, *J* 8 Hz, 11c-H), 4.45 (1 H, d, *J* 8 Hz, 11b-H), 4.76 (1 H, s, 4-H), and 7.05—7.48 (9 H, m, ArH); *m/z* (%) 332 (M^+, 13) and 221 (15).

2,3,3aα,4α,6,7,11bβ,11cα-*Octahydro isomer* (**42a**). Colourless prisms (methanol), m.p. 220—223 °C (decomp.) (Found: C, 75.8; H, 6.1; N, 8.7); $\nu_{max.}$(Nujol) 1 770, 1 690 (amide), 770, 745, and 700 cm^{-1}; δ(CDCl$_3$–[^{2}H$_6$]DMSO) 2.40 (1 H, m, 7-H), 2.85—3.24 (3 H, m, 6- and 7-H), 2.97 (3 H, s, 2-Me), 3.34 (1 H, t, *J* 8.5 Hz, 3a-H), 3.56 (1 H, d, *J* 8 Hz, 11c-H), 4.37 (1 H, d, *J* 9 Hz, 4-H), 4.98 (1 H, s, 11b-H), and 7.08—7.40 (9 H, m, ArH); *m/z* (%) 332 (M^+, 82) and 221 (M − 111, 100).

2,3,3aα,4α,6,7,11bα,11cα-*Octahydro isomer* (**43a**). Colourless, fine needles (methanol), m.p. 232—233 °C (Found: C, 76.1; H, 6.1; N, 8.25); $\nu_{max.}$(Nujol) 1 770, 1 700 (amide), 760, 745, 710, and 700 cm^{-1}; δ 2.30 (1 H, m, 7-H), 2.85—3.20 (3 H, m, 6- and 7-H), 2.80 (3 H, s, 2-Me), 3.50 (1 H, dd, *J* 7 and 9 Hz, 3a-H), 3.73 (1 H, t, *J* 6.5 Hz, 11c-H), 3.8 (1 H, d, *J* 9 Hz, 4-H), 3.91 (1 H, d, *J* 6 Hz, 11b-H), and 7.12—7.56 (9 H, m, ArH); *m/z* (%) 332 (M^+, 49) and 221 (100).

2,3,3aα,4β,6,7,11bβ,11cα-*Octahydro isomer* (**44a**). Colourless needles (methanol), m.p. 195—196 °C (Found: C, 76.1; H, 6.1; N, 8.2); $\nu_{max.}$(Nujol) 1 770, 1 690 (amide), 780, 770, 760, 750, 715, and 700 cm^{-1}; δ 2.40 (1 H, m, 7-H), 2.79 (1 H, m, 6-H), 2.95—3.20 (2 H, m, 6- and 7-H), 3.07 (3 H, s, 2-Me), 3.32 (1 H, dd, *J* 7 and 8 Hz, 3a-H), 3.48 (1 H, t, *J* 8 Hz, 11c-H), 3.75 (1 H, d, *J* 7 Hz, 4-H), 3.8 (1 H, d, *J* 8 Hz, 11b-H), and 7.1—8.0 (9 H, m, ArH); *m/z* (%) 332 (M^+, 93) and 221 (100).

2,3,3a,4,6,7,11b,11c-*Octahydro*-9,10-*dimethoxy*-2-*methyl*-4-*phenyl*-1H-*pyrrolo*[3′,4′:3,4]*pyrrolo*[2,1-a]*isoquinoline*-1,3-*dione* (**41b**)—(**44b**).—Prepared in an analogous manner to the above using 6,7-dimethoxytetrahydroisoquinoline-1-carboxylic acid (**35b**) and heating in DMF at 120 °C for 0.5 h. Flash chromatography of the crude isomer mixture eluting with 1:1 v/v toluene–ether gave (**44b**) (22%), (**41b**) (14%), (**42b**) (19%), and (**43b**) (15%) together with mixed fractions (8%).

2,3,3aα,4β,6,7,11bα,11cα-*Octahydro isomer* (**41b**). Colourless, fine needles (methanol), m.p. 181—184 °C (Found: C, 70.2; H, 6.3; N, 7.0. $C_{23}H_{24}N_2O_4$ requires C, 70.4; H, 6.2; N, 7.1%); $\nu_{max.}$(Nujol) 1 780, 1 710 (amide) 775, 750, and 705 cm^{-1}; δ 2.3—3.0 (4 H, m, 6- and 7-H), 2.9 (3 H, s, 2-Me), 3.58 (1 H, dd, *J* 1.5 and 8 Hz, 3a-H), 3.8 (1 H, t, *J* 8 Hz, 11c-H), 3.82 (3 H, s, 9-OMe), 3.93 (3 H, s, 10-OMe), 4.42 (1 H, d, *J* 8 Hz, 11b-H), 4.73 (1 H, d, *J* 1.5 Hz, 4-H), 6.52 (1 H, s, 8-H), 6.97 (1 H, s, 11-H), and 7.25—7.4 (5 H, m, ArH); ^{1}H NOEDSY: irradiation of 3a-H caused enhancement of 4-H (4%) and 11c-H (11); irradiation of 4-H caused enhancement of 3a-H (4); irradiation of 11-H caused enhancement of 11b-H (4) and 11c-H (6); irradiation of 11b-H caused enhancement of 11-H (6) and 11c-H (12); *m/z* (%) 392 (M^+, 44) and 281 (100).

2,3,3aα,4α,6,7,11bβ,11cα-*Octahydro isomer* (**42b**). Colourless, fine needles (methanol), m.p. 171—174 °C (Found: C, 70.5; H, 5.95; N, 7.0); $\nu_{max.}$(Nujol) 1 770, 1 700 (amide), 775, 750, and 700 cm^{-1}; δ 2.25—3.20 (4 H, m, 6- and 7-H), 2.99 (3 H, s, 2-Me), 3.38 (1 H, t, *J* 9 Hz, 3a-H), 3.53 ((1 H, d, *J* 8 Hz, 11c-H), 3.88 (3 H, s, 9-OMe), 3.93 (3 H, s, 10-OMe), 4.38 (1 H, d, *J* 8 Hz, 4-H), 4.96 (1 H, s, 11b-H), 6.6 (1 H, s, 8-H), 6.8 (1 H, s, 11-H), and 7.2—7.43 (5 H, m, ArH); ^{1}H NOEDSY: irradiation of 3a-H caused enhancement of 4-H (10%); irradiation of 4-H caused enhancement of 3a-H (16); irradiation of 11-H caused enhancement of 11b-H (5) and 11c-H (21); irradiation of 11b-H caused enhancement of 4-H (1), 11-H (3), and 11c-H (4); irradiation of 11c-H caused enhancement of 11-H (20) and 11b-H (5); *m/z* (%) 392 (M^+, 33) and 281 (100).

2,3,3aα,4α,6,7,11bα,11cα-*Octahydro isomer* (**43b**). Colourless, fine needles (methanol), m.p. 238—239 °C (Found: C, 70.2; H, 6.2; N, 7.0); $\nu_{max.}$(Nujol) 1 770, 1 690 (amide), 775, 760, 710, and 705 cm^{-1}: δ 2.18—3.06 (4 H, m, 6- and 7-H), 2.8 (3 H, s, 2-Me), 3.49 (1 H, dd, *J* 8 and 9 Hz, 3a-H), 3.7 (1 H, dd, *J* 7 and 8 Hz, 11c-H), 3.8 (1 H, d, *J* 9 Hz, 4-H), 3.85 (1 H, d, *J* 7 Hz, 11b-H), 3.86 (3 H, s, OMe), 3.96 (3 H, s, OMe), 6.63 (1 H, s, 8-H), 7.03 (1 H, s, 11-H), and 7.23—7.4 (5 H, m, ArH); ^{1}H NOEDSY: irradiation of 3a-H caused enhancement of 4-H (6%), 11b-H (2), and 11c-H (7); irradiation of 11c-H caused enhancement of 3a-H (6), 8-H (7) and 11b-H (3.4); *m/z* (%) 392 (M^+, 26) and 281 (100).

2,3,3aα,4β,6,7,11bβ,11cα-*Octahydro isomer* (**44b**). Colourless needles (ethanol), m.p. 216—217 °C (Found: C, 70.6; H, 6.2; N, 7.0); $\nu_{max.}$(Nujol) 1 765, 1 690 (amide), 790, 750, 720, and 710 cm^{-1}; δ 2.37 (1 H, m, 7-H), 2.68 (1 H, m, 6-H), 2.99 (2 H, m, 6- and 7-H), 3.07 (1 H, s, 2-Me), 3.32 (1 H, dd, *J* 7 and 9 Hz, 3a-H), 3.45 (1 H, t, *J* 9 Hz, 11c-H), 3.52 (1 H, d, *J* 9 Hz, 11b-H), 3.6 (1 H, d, *J* 7 Hz, 4-H), 3.87 (3 H, s, OMe), 3.98 (3 H, s, OMe), 6.64 (1 H, s, 11-H), 7.26—7.53 (5 H, m, ArH), and 7.64 (1 H, s, 8-H); ^{1}H NOEDSY: (250 MHz, 1:1 v/v CDCl$_3$–C$_6$D$_6$); irradiation of 4-H caused enhancement of 11b-H (9%); irradiation of 11b-H caused enhancement of 4-H (8) and 11c-H (2); irradiation of 11c-H caused enhancement of 3a-H (9) and 11b-H (2); (400 MHz) irradiation of 3a-H caused enhancement of 4-H (1.4), 11b-H (2), and 11c-H (6); *m/z* (%) 392 (M^+, 61) and 281 (100).

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